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Neuroimaging

Principal Investigator: ANDERSON, MARJORIE
Grant Number: 5R01NS044565-03
Title: Deep Brain Stimulation in Parkinson's Models

Abstract: Although high-frequency deep brain stimulation (HF-DBS) in the globus pallidus or subthalamic nucleus has become a common technique used to treat drug-resistant symptoms of Parkinson's disease, the mechanisms by which HF-DBS exerts its effects are unknown. In the proposed studies, the ability of chronic administration of the insecticide rotenone, to produce an animal model of Parkinson's disease will first be tested in monkeys. Using PET imaging now available in the University of Washington Regional Primate Research Center, changes in dopamine innervation after administration of rotenone will be measured using a marker of the monoamine vescicular transporter that is present in dopaminergic nerve terminals. These changes will then be correlated, over time, with changes in behavior and with electrophysiological changes in the rate and pattern of discharge of neurons in basal ganglia-receiving areas of the thalamus. This model will then be used to couple the electrophysiological effects of HF-DBS, which can be recorded from basal ganglia-receiving neurons of the thalamus, to the stimulation-induced changes in regional metabolism in the cortex and thalamus. PET imaging with the metabolic marker, [8-F] flurodeoxyglucose (FDG), will be used to measure metabolism. This technique has generally shown a relative hypermetabolism in the globus pallidus and thalamus of humans with Parkinson's disease and a relative hypometabolism in areas of the frontal cortex. Changes reported to be induced by HF-DBS have been mixed however. The combination of electrophysiology and metabolic imaging will allow us to address some of the discrepancies from the human literature. Special attention will be paid to the development of abnormal patterns of bursting behavior in the thalamus of monkeys treated with rotenone, as well as the effect of HF-DBS on burst behavior. This will test the hypothesis that some of the symptomatology of Parkinson's disease, and its relief using HF-DBS, is a consequence of abnormal patterns of activity in basal ganglia-thalamic-cortical circuits.-

Principal Investigator: ASHE, JAMES
Grant Number: 2R01NS040106-05
Title: Learning in the human motor cortex

Abstract: The long-term objective of this proposal is to understand how the brain learns and control movement sequences. As Lashley recognized more than half a century ago, much of our behavior, from the performance of organized movements to the ability to use language, is based on our capacity to detect, learn, and produce sequences. In the current proposal, we use variants of the serial reaction time (SRT) task and functional imaging in human subjects to examine the neural substrates responsible for learning the fundamental structure of movement sequences, the brain areas responsible for modulating learning through reward and punishment, and the extent to which the brain uses similar strategies for learning temporal and spatial sequences. We will test the following hypotheses. (1) During sequence learning cortical motor areas detect and learn transitions from one element to the next, while the basal ganglia encode the whole structure of sequenced movements. (2) Reward and punishment have direct but differential effects on motor sequence learning and this will be reflected by proportional changes in the activity of the basal ganglia. (3) Learning sequences of temporal intervals will engage a similar set of brain areas to those involved in learning spatial sequences and will not involve the cerebellum. Impairment in the ability to produce sequences is an important component of the disability experienced by patients with Parkinson's disease. The work outlined here will provide a fundamental understanding of these disabilities and may lead to the development of strategies for rehabilitation and treatment of these patients.-

Principal Investigator: BURKE, ROBERT E
Grant Number: 2P50NS038370-06
Title: Mechanisms of dopamine neuron degeneration

Abstract: Parkinson's disease (PD) is a prevalent and disabling neurological disease characterized by the progressive loss of motor control due to the degeneration of dopamine (DA) neurons of the substantia nigra. Among neurodegenerative diseases, PD has served as a model for the development of novel therapeutic approaches: administration of neurotransmitter precursors (levodopa), cell implantation, and more recently, deep brain stimulation. As important and effective as these advances have been, they only relieve symptoms; none stop the progression of the disease. In order to develop therapies which halt the progression of the disease, we need to achieve a better understanding of the pathogenesis of DA neuron degeneration. This submission represents a competing continuation application for a Morris K. Udall Parkinson's Disease Research Center of Excellence awarded to Columbia University in 1999. This renewal consists of four projects devoted to a single integrating theme: to understand the molecular and cellular mechanisms of dopamine neuron degeneration. While there are many worthy hypotheses of pathogenesis, the subprojects of this proposal will focus on four major current themes in the pathogenesis of PD, related to the roles of: (1) Abnormal intracellular protein degradation; (2) Inflammatory pathways; (3) Programmed cell death (PCD); and (4) Oxidative injury. In Project 1, Dr Serge Przedborski will evaluate the role of cyclooxygenase 2 (COX2) and cytosolic phospholipase A2 (cPLA2) (Theme 2) in mediating dopamine neuron damage in the MPTP model of PD and in human brain samples. In Project 2, Dr David Sulzer will examine in astrocyte and neuron primary cultures the role of chaperone mediated autophagy in the degradation of proteins implicated in PD (Theme 1) and the effect of these proteins on catecholamine sequestration (Theme 4). In Project 3, Dr Robert Burke will use genetic techniques in animal models to examine the roles of the mixed lineage kinases, Akt and JNK in mediating PCD in dopamine neurons (Theme 3), and he will evaluate the functional role of ER stress in initiating cell death (Theme 1). In Project 4, Dr Lloyd Greene will continue to evaluate the functional role of genes identified in the current funding period by SAGE analysis as upregulated following neurotoxin exposure. He will continue his studies of the role of ER stress-related genes (Theme 1) and genes implicated in PCD (Theme 3) in PC12 cells and primary sympathetic neurons, and in living animal models (the latter in collaboration with Drs Burke and Przedborski). He will also examine these transcripts and their protein products in PD brain. -

Principal Investigator: CALLAWAY, JOSEPH C
Grant Number: 5R01NS042276-03
Title: Dendritic Role in Dopamine Neuron Firing

Abstract: Destruction or dysfunction of the dopaminergic neurons of the mesencephalon is believed to underlie a variety of disorders of movement, motivation and mentation, including Parkinson's disease, and schizophrenia. In those disorders, not accompanied by death of the dopaminergic neurons, it is likely that a disruption of the activity patterns of those neurons is an important component of the pathology. Dopaminergic neurons fire in stereotyped modes, controlled largely by calcium currents and by calcium-dependent potassium currents. We will employ calcium-imaging of single neurons injected intracellularly with calcium indicator during whole cell recording in slices visualized by infra-red DIC microscopy. This will allow simultaneous detection of membrane potential at the cell bodies of the dopaminergic neurons and detection of calcium entry in the cell body and dendritic tree. Current models of firing pattern generation by dopaminergic neurons differ in their predictions of the location of calcium entry, and our experiments allow a critical test of these models. Synaptic excitation and local dendritic excitation by applied glutamate or glutamate agonists will be used to test for the local control of dendritic calcium currents by subthreshold excitatory currents. We will measure how action potentials propagating into dopamine cell dendrites contribute to slow oscillations in dendritic calcium levels and resulting calcium dependent potassium current that ultimately control the output firing pattern. Experiments will examine how the extent of dendritic spike propagation regulates pacemaker firing rate and whether modulation of dendritic spike propagation contributes to irregular and burst firing. Calcium channel blockers will be used in conjunction with calcium imaging to establish the types and distribution of calcium channels that contribute to voltage dependent calcium imaging to establish the types and distribution of calcium channels that contribute to voltage-dependent calcium entry in these cells. Finally, immunocytochemistry using antibodies against clones of channel subtypes will also be used to examine the distribution of calcium and calcium dependent potassium channels in the dendritic arbors of dopamine cells and results from will be compared to those from calcium imaging. -

Principal Investigator: ELSINGER, CATHERINE L
Grant Number: 1R43NS049705-01
Title: fMRI Evaluation of Parkinson's Disease

Abstract: Parkinson's disease (PD) is a progressive and incurable neurological disease affecting an estimated 4 million people worldwide. Health care costs in the U.S. alone have been estimated in excess of $6B. While many FDA-approved therapeutic interventions (pharmaceutical, surgical and physiological) have become available for the management of the motor and cognitive complications associated with PD, the majority of interventions become less effective over time as the disease progresses. The challenge is to develop more effective and longer lasting treatments that alter the disease course in addition to managing symptoms. Identifying incremental therapeutic efficacy over existing treatments may be hindered by existing clinical outcome measures that suffer from relatively low reliability and sensitivity. The next wave of clinical trials, therefore, will likely require reliable and sensitive biological markers that correlate with clinical outcomes. In Phase I of this project, we propose to test the efficacy of functional magnetic resonance imaging (fMRI), as a biomarker for quantifying a therapeutic response in PD. Phase II will entail the development of a standardized neuroimaging platform based on proprietary technology to be implemented across wide range of MRI scanner platforms. This commercial platform will target academic medical centers, hospitals, and clinics, as well as the pharmaceutical industry, in order to facilitate the evaluation of therapeutic response in PD. -

Principal Investigator: ESKANDAR, EMAD N
Grant Number: 2K08NS041851-04
Title: Neostriatal Visual Processing & Initiation of Movement

Abstract: The basal ganglia are a group of subcortical nuclei that are important for motivation and motor control. Disorders of the basal ganglia lead to a variety of disabling movement disorders, the most common of which is Parkinson's disease. The input nuclei of the basal ganglia in primates include the caudate and putamen. The output nuclei include the Gpi and the substantia nigra pars reticulata. Other important nuclei include the substantia nigra pars compacta and the subthalamic nucleus. The input and output nuclei of the basal ganglia are joined by two distinct sets of connections, known as the "direct" and "indirect" pathways. The current model of basal ganglia function holds that the two pathways are in functional opposition and that activation of the direct pathway facilitates movement while activation of the indirect pathway inhibits movement. This explanation works well in empirically explaining what areas of the two pathways are overactive in movement disorders. For example, the Gpi and STN are overactive in PD and hence are effective targets for treatment. However, the nature of the interaction between the two pathways is poorly understood. Most recent models of the basal ganglia emphasize their role in suppressing unwanted movements although this has never been directly tested. Therefore, the primary goal of this research is to understand the role of the basal ganglia in suppressing unwanted movements by recording the activity of basal ganglia neurons in awake behaving primates trained in a movement suppression task. The second goal is to compare the data obtained in primate studies with information obtained by recording from the subthalamic nucleus and globus pallidus of patients undergoing surgery for the treatment of Parkinson disease. In this fashion we hope to understand the derangements of basal ganglia function which occur in PD and to devise better treatment strategies. This work will be conducted in the Department of Neurobiology at Harvard Medical School and in the Department of Neurosurgery at Massachusetts General Hospital.-

Principal Investigator: FEDEROFF, HOWARD J.
Grant Number: 5U54NS045309-03
Title: Parkinson's Disease Gene Therapy Study Group

Abstract: Parkinson's disease (PD) affects about 1 million people in North America. Medications, such as levodopa, and some surgical approaches are available for PD, but offer only symptomatic therapy. New information contribute to current optimism that gene therapy might correct the molecular disturbances of PD, alleviate the symptoms of the illness and/or in retarding disease progression. Setbacks in gene therapy for other diseases underscore the importance of a purposely deliberate and careful approach that demands substantial assurances of safety and potential efficacy in advance of human testing. It is this philosophy of conservatism that will characterize the activities of our group. A coordinated stepwise progression from basic research through exhaustive preclinical evaluation prior to clinical testing is required. A multicenter, multidisciplinary collaborative group (The PD Gene Therapy Study Group [PDGTSG]) has formed and seeks support for those activities that will lead to a large-scale clinical trial of gene therapy for patients with PD. The PDGTSG consists of three different components: Cores, Principal Projects, and Pipeline Projects. Core A. Administrative Core (PI: Dr. Federoff): Houses a Steering Committee, and Vector (Chair: Dr. Lowenstein), Human Subjects/Clinical Assessment (Chair: Dr. Kurlan), Bioethics (Chair: Ms. Greenlaw), Intellectual Property (Chair: Ms. Hunter) and Biostatistics Modules (Chair: Dr. Oakes). Provides for the coordination of budgeting, committee scheduling, reports, progress preparation, and interface with NINDS staff, the clinical, scientific and lay community. Core B. Biological Measurement Core (PI: Dr. Federoff: Functions in the application shared quantitative measurements. Houses the database and the bank of vector constructs used in all studies. Project I. "Enzymatic Gene Transfer in MPTP Monkeys" (PIs: Bankiewicz and Kordower) Will comprehensively evaluate two vector platforms (rHIV and rAAV), each transducing the identical AADC gene cassette in the standardized non-human primate model. Project II. "Trophic Gene Transfer in MPTP Monkeys" (PIs: Bankiewicz and Kordower) Will comprehensively evaluate two vector platforms (rHIV and rAAV), each transducing the identical regulated GDNF gene cassette in the standardized non-human primate model. PIPELINE PROJECTS 0PPs) Focus 1: 1reproved regulation of gene expression PP I. "Tet-Regulated Vectors for Parkinson's Disease" (PI: Bohn). PP II. "Engineering RNA Switches that Respond to Dopamine and its Analogs" (PI: Breaker). Focus 2: Development of new vector platforms for application in PD disease models. PP III. "High Capacity Gutless Adenovirus" (PI: Lowenstein). PP IV. "Development of Integrating HSV

Principal Investigator: FREY, KIRK A
Grant Number: 5P01NS015655-24
Title: PET Study of Biochemistry and Metabolism of the CNS

Abstract: This Program Project focuses on in vivo neurochemistry of human neurological disorders, emphasizing subcortical structures and their interactions in neurodegenerative and idiopathic functional disorders of movement. Studies in the proposal combine neurochemical phenotypes with functional measures, the latter including motor performance, blood flow activation, neurotransmitter release, ans aspects of sleep physiology. The Program consists of 4 Scientific Projects and 3 Cores. Project by Kilbourn, "New Radiotracers for Neurological PET", will introduce a novel functional approach to assessment of GABAA receptors through allosteric ligands of the chloride ionophore. GABAergic projects are critical components of striatal output and other extrapyrimidal sites. Assessment of GABAA function will complement glucose metabolism studies that may preferentially reflect excitatory glutamatergic pathways. Project by Frey, "Striatal Dopamine and Motor Performance in Aging and Parkinson's Disease" will determine functional motor correlates of nigrostriatal dopaminergic losses in aging and Parkinson's disease and will assess their reversal by acute dopaminergic challenge. Project by Gilman, "Neurochemical and Sleep Disorders in Multiple System Atrophy", will assess the relationships between disrupted sleep in extrapyrimidal neurodegeneration and brain stem cholinergic projections. Project by Albin, "Dopamine Synaptic Mechanisms in Tourette Syndrome", will assess striatal dopaminergic projects and their function from a multi-faceted approach, including measures of their density, their capacity for dopamine re-uptake, their capacity for dopamine release, and an assessment of ambient synaptic dopamine occupancy of D2-type dopamine receptors. Cyclotron/Radiochemistry, Tomography and Data Analysis, and Administrative Core functions support each Project. Overall , the disorders under study in this Program are of unknown pathogenesis and have only symptomatic therapies. The proposed studies will lead to enhanced insight into extrapyrimidal neurochemistry and will address important aspects of dysfunction and disability in these disorders. Novel and improved therapies and new pathophysiological mechanisms and insight may ultimately result. -

Principal Investigator: Goldstein, David
Grant Number: 5Z01NS002979-06
Title: Clinical Neurocardiology: Catecholamine Systems In Stress And Disease

Abstract: Unavailable

Principal Investigator: GROSSMAN, MURRAY
Grant Number: 5R01NS035867-07
Title: Cognitive Impairments in Parkinson's Disease and Aging

Abstract: We seek converging evidence from cognitive studies of non-demented patients with Parkinson's disease (PD), electrocortical event-related potentials (CEPs), and functional magnetic resonance imaging (fMRI) to test our interactive neurocognitive model of core cognitive processes and executive resources in comprehension. Specific Aim 1 manipulates executive resources (working memory, strategic planning, inhibitory control) in ambiguous sentences. PD patients' impaired sentence comprehension will be related to limitations in specific executive resources. Resource-related slowing of CEPs will be seen in PD for the same material. fMRI in young subjects with this material will recruit interactive neural networks for sentence processing: left ventral inferior frontal cortex (vIFC) and left posterolateral temporal cortex (PLTC) for core language processes, and specific cognitive resources in left dorsal IFC (dIFC), prefrontal cortex, striatum, and right PLTC. To compensate for age- and disease-related resource limitations, healthy seniors and PD patients will up-regulate resource-related networks, but we expect no change in the core sentence processing network. Specific Aim 2 tests a material-neutral deficit for rules that depends on implicit memory. We examine regular and irregular morphology in verbs and nouns, and assess non-linguistic concept acquisition mediated by implicit- or rule-based learning. PD patients will show a material-specific deficit for rules in verbs. fMRI in young subjects will recruit left vIFC only for regular verb morphology, and dIFC for decision-making resources. d]FC will be up-regulated in aging and PD. Specific Aim 3 assesses the generalizeability of our model to prosody comprehension. PD patients judge acoustically simple and complex prosody stimuli at baseline and during a secondary task. Restricted resources will limit PD patients' comprehension of complex prosody. fMRI in young subjects will recruit orbital frontal and dIFC only for complex prosody, and dIFC will be up-regulated in aging and PD. Our data support a componential neurocognitive architecture consisting of dynamically interactive networks modified to process sentences depending on available resources and relative demand. -

Principal Investigator: Hallett, Mark
Grant Number: 5Z01NS002669-20
Title: Physiological Analysis Of Voluntary Movement

Abstract: Unavailable

Principal Investigator: HERSHEY, TAMARA G
Grant Number: 5K23NS041248-04
Title: Dopaminergic Modulation of Working Memory in PD

Abstract: The applicant is a clinical neuropsychologist with graduate training in neuropsychology and postdoctoral training in neuropharmacology and positron emission tomography (PET). The goal of this career development award is to integrate and advance these two areas of interest to answer questions about the neuropharmacological and neurophysiological basis of cognitive dysfunction in movement disorders such as Parkinson's disease (PD). This award will provide the applicant with training in the technical and theoretical issues related to using cognitive and pharmacological activation techniques in functional magnetic resonance imaging (fMRI). Long-term objectives are to address questions about the neural basis of cognitive dysfunction in movement disorders related to dopaminergic and/or basal ganglia dysfunction, such as PD, Tourette's syndrome and Huntington's disease. In addition, questions about the effects of dopaminergic treatments for these and other disorders (e.g. dystonia) on cognitive and neurophysiological functioning are also of interest. Cognitive dysfunction in these diseases, either due to the disease process itself or its treatments, can be limiting and disabling. Understanding the neurophysiologic basis for these symptoms may aid in assessing the effectiveness of current treatments or in developing better treatments. During the award period, the applicant will develop expertise in the use of fMRI, cognitive and neuropharmacological techniques to study these disorders, and will continue to hone her clinical skills in the neuropsychological assessment of movement disorders. The applicant will apply these new techniques to investigate the role of dopamine in working memory. The specific aims of the proposed studies are to test the hypothesis that 1) PD affects prefrontal cortex involvement in working memory and 2) dopaminergic modulation of working memory primarily occurs due to changes in lateral prefrontal cortical activity. To test these hypotheses, the applicant will first perform a behavioral study examining the effects of a steady-state infusion of levodopa, a dopamine precursor, on verbal and spatial working memory in PD patients and controls. The results of this study will then guide the choices of working memory tasks for an fMRl study. Subjects will be asked to perform working memory tasks before and during a steady-state infusion of levodopa. Modulation of the lateral prefrontal cortex is predicted during levodopa infusion. The degree of modulation is predicted to depend on baseline dopaminergic status (PD vs control) and the degree of memory load (low vs high). -

Principal Investigator: HOLLOWAY, ROBERT G
Grant Number: 5K24NS042098-04
Title: Neurology Outcomes Research:Clinical Trials/ Training

Abstract: New insights into the pathogenesis of Parkinson's disease (PD), the availability of a wider array of anti-parkinsonian therapies, the evolution of better tools for evaluating and monitoring disease progression have combined to change the current management of PD and the future landscape of PDrelated therapeutic clinical trials. This proposal outlines the key initial steps to develop the clinical trial methodology that allows for the longterm assessment of quality of life and economic outcomes in chronic neurological conditions. This will be accomplished by extending the duration of large multicenter clinical trial of pramipexole versus levodopa in early PD and augmenting the data collection effort to include clinical, quality of life, economic, and functional imaging outcomes. This will address questions for patients and providers on the best approach to treating early PD, as well as to provide a multidisciplinary research platform (clinical trials, quality of life assessment, and economic evaluation) to train a growing number of physician faculty and fellows at the University of Rochester in the theoretical, methodological, and practical knowledge and skills for a productive career in patient-oriented research. Dr. Holloway's position within the Departments of Neurology and Community and Preventive Medicine, and the Rochester Clinical Research Curriculum will ensure the recruitment of highly qualified trainees. -

Principal Investigator: HOLROYD, SUZANNE
Grant Number: 5R01NS045008-02
Title: Parkinsons disease:Visual dysfunction and hallucinations

Abstract: The purpose of this three year grant is to examine the relationship between visual hallucinations and visual system abnormality in Parkinson's disease. Visual hallucinations are common symptoms and frequent causes of morbidity in Parkinson's disease, yet little is known about their etiology. Increasing evidence suggests that hallucinations in Parkinson's disease are not simply a medication effect, but are associated with the underlying disease process. Specificallly, evidence exists that suggest visual hallucinations in Parkinson's disease may be related to known visual system dysfunction in Parkinson's disease. In this study, thirty Parkinson's disease patients with visual hallucinations will be matched to thirty Parkinson's disease patients without visual hallucinations. They will be examined on neuropsychological tests assessing visual cognitive function, and will undergo visual evoked potentials. A subset of these patients (20 matched pairs) will also undergo functional magnetic resonance imaging (fMRI) to assess visual cortex function. It is hypothesized that Parkinson's disease patients with visual hallucinations will have greater evidence of visual system abnormality. Specifically they will demonstrate greater deficits of visual-cognitive function, greater latency on visual evoked potential and differences in activation of visual cortical regions on functional magnetic resonance imaging (fMRI) than those without visual hallucinations. It is hypothesized that these results will support a proposed biologic model of VH in PD regarding the role of dopamine abnormality in both the retina and basal ganglia that effect the regulation of function of visual cortex. The results of this study will increase knowledge regarding the neural mechanisms of visual hallucinations in Parkinson's disease and knowledge of visual system abnormality in Parkinson's disease. The results may also increase our understanding of visual hallucinations in other disorders. Conceivably, such knowledge could lead to strategies to prevent, minimize or treat such symptoms.-

Principal Investigator: HORTOBAGYI, TIBOR
Grant Number: 1R13NS047105-01
Title: International Symposium on Motor Control Using TMS

Abstract: This application is a single-year request of support for an international symposium, "Mechanisms of Movement and Sensation Using Transcranial Magnetic Stimulation" (TMS) as part of the XVth biennial Congress of the International Society of Electrophysiology and Kinesiology (ISEK), Boston, June 18-21, 2004. The rationale for the symposium is that in this era of specialization, research subdisciplines on the one hand and basic researchers and therapists on the other, tend to separate. This symposium is an effort to minimize this separation. The symposium's aim is to generate a novel synthesis of basic science and clinical mechanisms of motor cortex plasticity and thus facilitate the design of rehabilitation programs. Pascual-Leone, co-chair, (US), will provide a historical perspective on TMS and rTMS. Valero Cabre (US) will discuss the effects of TMS and rTMS on the basic electrophysiological and metabolic properties of cortical neurons with reference to Parkinson's disease. Hortobagyi (US) will discuss the contralateral organization of the human nervous system. Taylor (Australia) will address the mechanisms of central fatigue in polio and chronic fatigue syndrome. Sawaki (US) will present on training dependent plasticity of the motor cortex as evidence for short-term motor memory, specifically in stroke. Rothwell (UK) will address the effect of afferent input on motor cortex organization and plasticity in healthy subjects and in patients with dystonia and hand cramps. Manto (Belgium) as co-chair will moderate the discussions. The symposium will provide maximal interaction between speakers and attendees as it will take place in a plenary session format as the only ongoing session. Through student discounts, it will provide an economical opportunity for biomedical trainees to attend. The presentations will be published in IEEE Engineering in Medicine and Biology, making a substantial impact on the field by attracting the interest of neurologists, clinical neurophysiologists, basic and clinical movement and sensation neuroscientists, physical therapists, biomechanists, biomedical engineering researchers, roboticists, educators and students from the US and abroad.-

Principal Investigator: ISACSON, OLE
Grant Number: 5R01NS041263-05
Title: ANTI-INFLAMMATORY THERAPIES NEUROTOXICALLY INDUCED PD

Abstract: A recent large Parkinson's Disease (PD) twin study indicates that environmental and toxic factors play major roles in causing typical PD (Tanner, et. al. JAMA, 1999). Interestingly, neuroinflammation seen in the caudate-putamen is a part of the pathophysiology (Brooks, 1999). The progressive decline of dopamine (DA) terminals seen in idiopathic PD can be closely modeled in Macaca fascicularis by low-dose exposure to the mitochondrial toxin, MPTP, over nine to fourteen months. The investigators demonstrated by PET imaging of DA terminal and MRS that such primates provide a physiological chart of degeneration and appearance of PD signs (Brownell, et. al., Nat. Med., 1998). This data profile enables the design of an experimental paradigm for realistically determining toxicity, neuroinflammation and neuroprotection in idiopathic PD. In this project using the PD primate model, the investigators now propose to examine neuroprotection of the dopaminergic system by anti-inflammatory agents. Based on several studies, they hypothesize that a cyclooxygenase (COX) 1 and 2 inhibitor (indomethacin [1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1-H-indole-3-acetic acid]) can decrease inflammatory reactions caused by MPP+ toxicity and also reduce chronic neurodegenerative processes. In the non-human primate, a slow progressive lesion of the nigrostriatal dopaminergic system follows repeated MPTP treatment. Using PET scanning with a receptor ligand for the peripheral benzodiazepine receptor site (11-C-PK1 1195), preliminary experiments indicate that they can visualize the neuroinflammatory reactions during CNS DA degeneration (as determined by 11-C-CFT). These measurements will be combined with MRI and MRS studies of lactate and choline as in vivo biomarkers for the glial inflammatory and toxic responses of the nigrostriatal system. As a therapy, during and after neurotoxic exposure to MPTP, the investigators will treat the PD primates with a COX I and 2 inhibitor to evaluate anti- inflammatory prevention of onset and continued degeneration. Protection of the dopaminergic system by anti-inflammatory agents would be of tremendous therapeutic value for PD. -

Principal Investigator: ISACSON, OLE
Grant Number: 3P50NS039793-05S1
Title: NOVEL THERAPEUTIC APPROACHES FOR PARKINSON'S DISEASE

Abstract: Unavailable

Principal Investigator: JAHANSHAHI, MARJAN
Grant Number: 5R01NS040865-04
Title: DEEP BRAIN STIMULATION--COGNITION/MOTIVATION/MOOD IN PD

Abstract: Deep brain stimulation (DBS) of the subthalamic nucleus (STN) has been shown to be an effective treatment for the motor symptoms of Parkinson's disease (PD), particularly improving akinesia and rigidity and reducing levodopa-induced dyskinesias. Neuropsychological investigations have shown that such beneficial effects of DBS on motor function are accompanied by significantly worse performance on specific tests of cognitive executive function such as word fluency and conditional associative learning, respectively when assessed after relative to before surgery or with stimulation on vs off. Surgery for DBS has also been reported to be associated with improvements of depression and anxiety, possibly as a result of the improved motor function, but also some loss of initiative and fatigue suggestive of apathy, a motivational deficit. DBS of the STN is based on current models of fronto-striatal functioning in normals and in PD. The proposed project will involve a more detailed investigation of the impact of DBS on specific tests of executive function (word fluency, random number generation) and learning (conditional associative learning, motor sequence learning) and on mood and motivation using a series of clinical neuropsychological and PET activation studies. The specific aims are: 1.To conduct a number of clinical neuropsychological studies to compare the effects of stimulation on vs off and determine whether DBS results in significant deterioration on tests of cognitive executive function such as word fluency and on tests of learning such as conditional associative learning and motor sequence learning and to clarify the precise nature of the deficits on these tests with stimulation. The impact of DBS on mood and motivation will also be assessed before and 3 months after surgery using a series of standardized questionnaires and interview schedules and the association of these changes to changes in disability and quality of life will also be investigated. 2.To use PET activation studies to identify the mechanisms of change in executive function and learning with DBS of the STN in PD. The effect of stimulation on vs off on regional cerebral blood flow will be measured while patients perform tests of executive function (phonemic word fluency or random number generation), learning (conditional associative learning or motor sequence learning) or matched control tasks and during a choice RT with or without manipulation of motivation (provision of feedback and incentive for fast responses). Any changes in frontal and striatal activation and in fronto-striatal connectivity within and between the motor, associative and limbic circuits will be measured using techniques such as structural equation modeling and regression methods to

Principal Investigator: JENNINGS, DANNA L
Grant Number: 5R44NS043826-03
Title: An Imageing Marker for Parkinson's Disease

Abstract: The development of disease modifying agents in Parkinson's disease has rapidly expanded the need for in vivo markers for diagnosis and monitoring disease progression. Dopamine transporter (DAT) imaging offers the promise of an objective measure of dopaminergic degeneration allowing for identification of changes in the brain that occur early in the illness, prior to clinical diagnosis. The primary goal of this project is to examine the sensitivity and specificity of DAT imaging using [123I]beta-CIT and SPECT imaging as a diagnostic marker in subjects with suspected PD or PS. We have successfully completed the Phase I pilot study for this project and have utilized these data and experience in designing this Phase II SBIR proposed protocol. The overall study design is to recruit subjects with suspected PD from participating community neurologists and compare the baseline diagnoses of the community neurologists, movement disorders experts and dopamine transporter imaging to a 'gold standard' clinical diagnosis assigned by a movement disorder expert at 12 months follow-up. The DAT imaging diagnosis will be compared to the 'gold standard' clinical diagnosis to determine the sensitivity of [123I]beta-CIT and SPECT imaging as a diagnostic marker in PD and PS. This project is a crucial step to begin to establish [123I]beta-CIT and SPECT imaging as an objective diagnostic biomarker prior to a definitive diagnosis in patients with early parkinsonian symptoms. -

Principal Investigator: LANGE, NICHOLAS T
Grant Number: 2R01NS037483-06A1
Title: Biostatistical Methods for Human Brain Mapping

Abstract: This is a continuing proposal to address a variety of biostatistical problems motivated by current issues in imaging neuroscience, as during the previous funding cycle. New aims: the development of flexible semiparametric growth curve models for accelerated longitudinal designs; advancing methodology for replicated spatial point processes and 3-D brain brain cell assemblies; and new methods and algorithms for semiautomatic identification of human brain cells. We propose to generalize our proposed individual low-rank smooth regression methods to compositional data via a logit-Gaussian model within a hierarchical Bayes framework. We seek to produce practical guidelines for designing cost-effective longitudinal studies involving expensive outcomes measurements. We propose to advance Poisson random field methods for sparse processes, motivated by the multiple cell types and regional structures in the human brain. Empirical data analysis will continue to play a central role in the proposed research. Our human brain mapping research by magnetic resonance imaging (MRI) and positron emission tomography (PET) and human brain tissue microscopy again relates directly to the study of psychiatric and neurological outcomes in healthy and ill subjects, both young and old. Through our collaborating biostatistical and neuroscience institutions, our ongoing translational research develops and links modem biostatistical methods with complementary work in longitudinal anatomic human brain imaging, functional human brain imaging and human brain tissue microscopy. Brain diseases addressed are schizophrenia, bipolar disorder and Parkinson's disease. However, potential applications of our methods go well beyond human brain mapping to include longitudinal and spatial epidemiology, risk assessment, health policy and management, nutrition, and other fields in which cost and feasibility constraints impose restrictions on the numbers of subjects studied and on the numbers and timings of their repeated measurements.-

Principal Investigator: MENTIS, MARC J
Grant Number: 5K23NS002204-05
Title: MECHANISMS UNDERLYING THERAPY IN PARKINSON'S DISEASE

Abstract: The award is intended to develop the candidate's research skills in, psychophysics, pharmacology, and advanced functional imaging (systems analysis, and fMRI) to equip him for an independent career evaluating mechanisms underlying successful therapy of cognitive dysfunction in neurodegenerative diseases. Once identified, successful medical and/or surgical mechanisms can be manipulated to refine existing, and develop novel therapies. Research Plan: Parkinson's Disease (PD), expected to afflict 1,000,000 Americans by the year 2000, frequently exhibits cognitive deficits (dysexecutive syndrome) in non- demented PD patients, in addition to the 40% with dementia. While the deficits have been linked to frontal cortical dysfunction and/or a disorder of subcortico-frontal connectivity, the functional basis of these deficits in PD remains poorly understood. Dopamine replacement therapy, successful for the motoric signs of PD, falls to improve the dysexecutive syndrome. Pathological studies show 20% loss of cholinergic cells in subcortical nuclei of non-demented PD patients, abnormal cortical choline acetyltransferase, reduced cortical and subcortical nicotinic receptors, and a correlation between cortical nicotinic loss and cognitive dysfunction. Preliminary clinical reports suggest cognitive improvement with non-specific cholinergic therapy. In Specific Aim 1, the candidate proposes a PET study of PD patients performing kinematically-controlled motor learning and execution tasks at baseline and with cholinergic pharmacotherapy. The pharmacological technique will allow him to identify the contribution of receptor families (muscarinic and/or nicotinic) to cholinergic modulation of specific brain networks known to be associated with learning performance. Based on these results, the candidate will test the hypothesis that nicotinic therapy will improve defined aspects of cognitive dysfunction in PD. The candidate wishes to bridge the gap between clinical of cognitive abnormality, and pathological observation of cholinergic loss, firstly, by quantifying the modulation of cholinergic receptor families on brain networks subserving cognition, then by testing if predicted improvements occur with therapy of a particular receptor family. In Specific Aim 2, the candidate will expand upon a preliminary observation that deep brain stimulation (DBS) may improve learning performance in PD. He will perform a PET study on PD patients on and off subthalamic nucleus (STN) DBS to determine the effect of therapeutic stimulation on the same tasks as in Specific Aim l. This will test the hypothesis that STN DBS may enhance cognitive performance in PD by modulating the expression of subcortico-frontal projection

Principal Investigator: Oldfield, Edward
Grant Number: 5Z01NS002854-13
Title: Pathophysiology Of Neurosurgical Disorders

Abstract: Unavailable

Principal Investigator: PERLMUTTER, JOEL S
Grant Number: 2R01NS041509-04
Title: MECHANISM OF DEEP BRAIN STIMULATION

Abstract: Deep brain stimulation (DBS) of the subthalamic nuclei (STN) may provide substantial reduction of symptoms in people with Parkinson disease (PD) and DBS of the thalamic ventral intermediate nucleus (VIM) markedly reduces tremor in people with disorders such as essential tremor (ET). Increasing data also indicates that STN DBS in PD may produce unwanted cognitive impairments, such as impairments of spatial delayed recall or response inhibition. Despite these dramatic clinical effects, the precise mechanism of action of DBS remains unclear. Recent studies, including several from this lab, indicate that DBS produces a net increase in neuronal output from the site of stimulation either the STN in PD or VIM in ET, and there may be important differences in the effects of STN on the left and right sides of the brain. Nevertheless, how this action and its asymmetry provide clinical benefit while simultaneously interfering with selected cognitive function remains unknown. We hypothesize that STN and VIM DBS provide motor benefit by altering function of specific motor brain regions, whereas, STN DBS impairs cognitive skills by altering function of selected prefrontal regions. Further, we propose that there are substantial differences between left and right-sided STN stimulation on aspects of motor and cognitive function. We will test these specific hypotheses using PET to measure brain blood flow responses to varying levels of STN or VIM stimulation in people with PD or ET and then correlate these PET responses with cognitive or motor responses to DBS in the same subjects. These studies have the potential to reveal valuable insights into the mechanism of DBS and also into the pathophysiology of these diseases and their clinical manifestations. For example, we may identify specific brain pathways that mediate cognitive impairment from STN DBS that are distinct from those that mediate motor benefit. This could directly lead to designing new strategies to maximize motor benefit and minimize cognitive impairments. We also have the potential to provide a rationale for investigating new sites for DBS that may be more accessible than those currently used. This innovative study brings together rigorous, carefully controlled PET investigations with quantified motor and cognitive behavioral measures.-

Principal Investigator: POWERS, WILLIAM J
Grant Number: 5R01NS041771-04
Title: CEREBRAL MITOCHONDRIAL METABOLISM IN NEURODEGENERATION

Abstract: Several lines of evidence suggest that Huntington's disease (HD) and Parkinson's disease (PD) have defects in mitochondrial function that impair oxidative phosphorylation and play a key role in the mechanism of neuronal death. To date, however, there have been no direct measurements of cerebral oxygen to glucose metabolic ratios to demonstrate an in vivo defect in cerebral mitochondrial metabolism in these diseases. We will use positron emission tomography (PET) to measure in vivo regional cerebral oxygen metabolism (CMR02) and cerebral glucose metabolism (CMRglc) to test two primary hypotheses: 1) Patients with HD have a generalized defect in cerebral mitochondrial metabolism. To test this hypothesis, we will measure whole brain CMR02/CMRgIc in 15 gene-positive pre-symptomatic patients with HD, 15 gene-positive patients with HD and definite motor signs and 30 age/gender-matched normal controls. 2) Patients with PD have a generalized defect in cerebral mitochondrial metabolism. To test this hypothesis, we will measure whole brain CMR02/CMRgIc in 15 never-medicated, early PD patients and 15 age/gender-matched normal controls. In the same subjects, we also will test two secondary hypotheses: 3) Regions vulnerable to pathologic insult have larger magnitude or selective defects in cerebral mitochodrial metabolism - caudate and putamen in HD and substantia nigra and putamen in PD. 4) In PD and HD, the degree of dysfunction in platelet electron transport complex function measured in vitro correlates with the degree of abnormal cerebral mitochondrial metabolism measured in vivo. At this time it is not clear how the abnormalities in electron transport chain activity measured in vitro in these two diseases correspond to cerebral mitochondrial metabolism in vivo. Direct in vivo regional PET measurements of CMR02 and CMRglc will allow us to demonstrate the extent and magnitude of mitochondrial dysfunction in vivo. Establishing the existence of cerebral mitochondrial dysfunction early in the course of these diseases will not only provide insights into the pathogenesis, but it will provide a measurable biological abnormality that can be monitored to determine the effect of treatments aimed at slowing or halting the progression of neuronal loss. The opportunity to determine the relation between platelet mitochondrial function and cerebral mitochondrial metabolism in patients with PD and HD is uniquely important. If such a relationship can be established in untreated patients in this study, then we would pursue further studies to determine the effects on cerebral mitochondrial metabolism of agents that alter platelet mitochondrial function. If such studies yield consistent results, they will establish the basis for

Principal Investigator: SCHNEIDER, JAY S
Grant Number: 2R01NS038681-06
Title: GM1 Ganglioside Effects on Parkinson's Disease

Abstract: Parkinson's disease (PD) is a slowly but relentlessly progressive neurodegenerative disorder resulting in a time-dependent worsening of clinical symptoms. No drug has yet been identified that definitively slows or stops the progression of PD or substantially forestalls the inevitable functional decline in PD patients. Thus, disease modifying drugs that can modify clinical progression, enhance repair of damaged neurons, remediate existing neuropathological deficits, restore or enhance function of residual parts of the dopamine (DA) system and/or activate compensatory mechanisms are sorely needed. GM1 ganglioside may be such a treatment. In vitro and in vivo studies have shown GM1 to rescue damaged DA neurons, stimulate survival and repair of DAergic neuron and sprouting of functional DAergic terminals, increase DA levels in the striatum and upregulate DA synthetic capacity of residual neurons. Preliminary clinical studies of GM1 in PD patients have shown clinical improvements in patients with short-term use of GM1 and minimal symptom progression in patients with 2 to 5 years of GM1 use with resumed progression of symptoms following discontinuation of long-term GM1 use. The specific aims of this research are: 1) Assess the clinical efficacy of GM1 and the relationship between clinical improvement and in vivo quantitation of the integrity of the striatal DAergic innervation (assessed by PET imaging of the dopamine transporter site) in patients with typical mild/moderate PD in a randomized double blind placebo-controlled clinical trial. Working hypothesis: GM1 ganglioside treatment will result in symptomatic improvements related to effects on damaged but viable DA neurons and this may be accomplished through sprouting of functional DAergic terminals in the striatum. 2) Assess the extent to which long-term (2 years) use of GM1 ganglioside may stabilize symptoms or slow symptom/disease progression in PD patients (using clinical evaluations and PET imaging of the dopamine transporter as a surrogate measure). Working hypothesis: Long-term GM1 use will stabilize symptoms or slow the progression of symptoms in PD patients and this may be accompanied by reduced loss of striatal DA terminals over time. -

Principal Investigator: Tanner, Caroline M.
Grant Number: 5R01NS040467-05
Title: TWINS AND RISK OF PD: A CLINICAL AND IMAGING STUDY

Abstract: The long-term goal of this research is to determine the relative contributions of genetic and environmental factors in the etiology of typical Parkinson's disease (PD) by comparing concordance rates in MZ and DZ twin pairs, at least one of whom has Parkinson's disease. This proposal extends our recent results in an irreplaceable cohort, the NAS/NRC World War II Veteran Twins cohort, which showed nearly identical concordance rates in monozygotic and dizygotic twin pairs with typical late onset (over age 50) Parkinson's Disease. These results strongly implicate environmental factors in the pathogenesis of Parkinson's disease, since one would expect monozygotic twins to show a much higher concordance rate than dizygotic twins if Parkinson's Disease were genetically determined. However, without follow-up we cannot be certain that unaffected cotwins would not have eventually developed the disease, thus changing the study outcome. We propose to assess the presence of both clinical parkinsonism and abnormal striatal dopamine function in twin pairs discordant for Parkinson's disease, and to compare concordance rates by zygosity. Aim 1 will determine if long-term follow-up will change Parkinson's disease concordance ratios in monozygotic and dizygotic twins. We expect to add at least 100 newly diagnosed twin pairs and to re-assess diagnosis in 140 prevalent discordant pairs. The second aim will be to compare the concordance rates in monozygotic twins and dizygotic twins, for either Parkinson's disease or abnormal striatal dopamine function as measured using dopamine transporter imaging with [123I]beta-CIT (2beta-carbomethoxy-3beta-(4-iodophenyl) and SPECT. In the third aim, we will compare concordance rates by zygosity for an abnormal rate of decline in striatal dopamine function. The mean annual decline in striatal dopamine uptake will be estimated by using [123I]beta-CIT uptake separated by, on average, two years. These studies, by virtue of utilizing both clinical and imaging measures, should determine clearly and beyond a doubt if the earlier twins study was flawed by virtue of missing pre-clinical cases of Parkinson's disease. This in turn could help set the research agenda on the cause of Parkinson's disease for years to come. -

Principal Investigator: VAILLANCOURT, DAVID E
Grant Number: 5F32NS044727-02
Title: fMRI Activity During the Visual Control of Force

Abstract: Functional magnetic resonance imaging (fMRI) at 3 Tesla provides a powerful tool to investigate the sensorimotor processes involved in the neural control of human movement. The long term objective of the investigator is to examine the neurophysiological processes, as measured by blood oxygenation level dependent (BOLD) contrast, involved in the motor control of healthy individuals and extend these paradigms to study the influence of intervention strategies (e.g. rehabilitation, pharmacology) on the physiology of aging and disease. The specific purpose of this proposal is to examine the neural systems underlying the spatial and temporal components of the mechanism that transfers visual signals into motor commands---a visuomotor process. The proposed studies will measure BOLD contrast fMRI and isometric force output from human participants while they perform continuous feedback-based force production. The experiments will examine two hypotheses in two specific aims. Aim 1 tests the hypothesis that the temporal component of the visuomotor process is localized in the parietal cortex and the cerebellum bilaterally. Aim 2 tests the hypothesis that the spatial component of the visuomotor process is also localized in the parietal cortex and the cerebellum bilaterally. It is further hypothesized that the spatial regions within the parietal cortex and cerebellum will be different from the temporal areas shown in Aim1. Collectively, these findings will advance our fundamental understanding of human systems neuroscience and improve feedback models of visuomotor control. These findings will have further implications for better understanding the visuomotor control deficits associated with aging, and diseased persons with Parkinson's disease, ataxia, and cerebellar deficits.-

Principal Investigator: VITEK, JERROLD L
Grant Number: 7R01NS037019-06
Title: Deep Brain Stimulation in the Parkinsonian Monkey

Abstract: Over the last decade, the outlook for patients with advanced parkinsonism and other movement disorders has been revolutionized by the introduction of deep brain stimulation (DBS) in the subthalamic nucleus (STN) and internal segment of the globus pallidus (GPi) as a highly effective treatment modality. According to recent estimates over 2000 patients with PD have undergone implantation of DBS electrodes for the treatment of PD and over 15,000 patients per year may be candidates for this procedure. This number will increase, as the use of DBS as treatment of brain disorders becomes more widespread. Despite their widespread use, very little is known about the physiologic effects of DBS. Given the somewhat similar effect of lesions and stimulation in STN, GPI and thalamus on parkinsonian motor signs, it has been speculated that stimulation may act similar to lesioning, by blocking neuronal activity. Several studies have supported this view reporting suppression of neuronal activity in the site of stimulation. Our preliminary results, as well as the results of other groups have suggested that stimulation may, in fact increase output from the stimulated structure, demonstrating that stimulation in the STN increases neuronal activity in the GPi, while GPi stimulation suppresses neuronal activity in the thalamus. Additional support for this hypothesis is derived from microdialysis studies that found increased levels of glutamate in the entopeduncular nucleus (the rodent equivalent of GPi in primates) during STN stimulation. Conceivably, stimulation of basal ganglia activity may improve parkinsonism simply by regularizing pallidal discharge patterns. Both activation and inactivation could, in fact, be invoked during stimulation, because electrical stimulation may inhibit neuronal activity, while activating fibers in the stimulated area. For further optimization of current DBS protocols, and to minimize risks and side-effects of DBS implantation, it is mandatory that a solid understanding of the mechanism of action of this intervention is developed. This study will determine the mechanism underlying the effects of DBS of STN and GPi by examining in the MPTP monkey model of PD: 1) the effect of stimulation in the STN and GPi on neuronal activity and on neurotransmitter release in different portions of the basal ganglia-thalamocortical circuit, 2) the role of GPe in mediating the effect of stimulation in the STN and GPI, in mediating the development of parkinsonian motor signs and as an alternative site for stimulation for the treatment of PD and 3) determine the effect of stimulation in the STN and GPI on cortical function. The experiments will use a combination of single cell recording, microdialysis, and 18F-fluoro-deoxy-glucose

Principal Investigator: WATERHOUSE, RIKKI N
Grant Number: 5R21NS041603-02
Title: Development of PET Radioligands for NMDA Receptors

Abstract: Unavailable

Principal Investigator: WU, ALLAN D
Grant Number: 1K23NS045764-01A1
Title: Motor cortex function in unimanual goal-directed aiming

Abstract: This research career development proposal describes a multidisciplinary mentored program allowing the investigator, Dr. Wu, to develop expertise in quantitative motor behavior research methods and transcranial magnetic stimulation (TMS). Dr. Wu will apply this expertise to further the understanding of mechanisms in normal motor control with the long-term goal being to establish how such mechanisms go awry in disease states such as Parkinson's disease (PD), dystonia and sensorimotor stroke. Dr. Wu is a neurologist with current clinical expertise in movement disorders and neurophysiology, who plans to develop a program exploring the research, neuromodulation and eventual treatment potential of TMS in movement disorders. He will be mentored by Dr. Winstein, who brings a quantitative motor behavior approach, as well as access to the support and resources necessary for development of a TMS-equipped neuro-motor physiology laboratory at USC. Drs. Iacoboni and Pascual-Leone will jointly supervise a customized TMS fellowship. Dr. Wu will perform experiments in a practical TMS setting at UCLA under the mentorship of Dr. Iacoboni, and will attend semiannual mini-fellowships at Beth Israel Deaconess Medical Center in Boston with Dr Pascual-Leone. Studies using TMS as a possible therapy for PD, often by targeting TMS over primary motor cortex (M1), have thus far shown inconsistent results, but may be limited by a relative absence of knowledge about how TMS affects normal motor control. Dr. Wu proposes to systematically investigate the effects of TMS over M1 on uni-manual goal-directed aiming movements, a fundamental unit of motor control. Two hypotheses are investigated: 1) The causal importance of M1 in the preparation of discrete aimed movements; and 2) the causal functional asymmetry of M1 for the execution of continuous aimed movements. Results may extend theories of aiming by placing a specific, functionally important, causal role of M1 for aspects of motor control. These studies will form a basis of the outlined career development plan for Dr. Wu from which extrapolation of findings in normal subjects to those with clinical movement disorders (such as PD) may lead to future rational selection of TMS parameters that can predictably and effectively modulate movement disorders symptoms. -

Principal Investigator: York, Michele
Grant Number: 5K23NS041254-03
Title: Cognitive functioning following deep brain stimulation

Abstract: Dr. Michele York, under the mentorship of Dr. Harvey Levin, Director of Research of Baylor College of Medicine's (BCM) Physical Medicine and Rehabilitation Department and Professor of Psychiatry and Neurosurgery, and Dr. Robert Grossman, the Chairman of BCM's Neurosurgery Department, will more effectively evaluate the long-term cognitive effects of deep brain stimulation (DBS) for the treatment of Parkinson's disease (PD). The scientific objective of the proposed research plan is to more clearly understand the relationship between the frontostriatal neural circuitry affected by DBS and PD and cognitive functioning. The clinical objectives of the proposed research plan include improving upon the evaluation of outcome by improving cognitive diagnostic techniques, clarifying the clinical criteria for surgical selection, and incorporating analysis of post-operative magnetic resonance imaging (MRI) findings. To achieve these aims, Dr. York will compare the executive functioning of patients undergoing staged bilateral subthalamic (STN) and globus pallidus (GPI) DEIS to patients who receive the best medical management for the treatment of PD on verbal fluency measures administered under conditions of set shifting and attentional control and working memory measures, which are cognitive processes dependent on the functional integrity of frontostriatal circuitry. The relationship between DBS electrode placement and performance on these frontostriatal neuropsychological tasks will also be investigated. The objectives of the training program are to acquire practical and technical skills that will aid Dr. York in developing her career, specifically in the areas of neurosurgical interventions and neurological evaluations of PD, structural and functional neuroimaging, and the neuroscience of PD. This training will provide Dr. York with a better understanding of the cognitive deficits in PD and the mechanisms and consequences of emerging interventions for the treatment of this neurological disease. The training activities during the award period will consist of 3 major components: 1) Didactics through coursework, technical training seminars, rounds, and observation, 2) Supervisory Guidance through regularly scheduled meetings with mentors and an Advisory Committee, and 3) Instruction in the Responsible Conduct of Research. Dr. York will gain the necessary knowledge to attain her long-term career goal of working as an independent clinical researcher by acquiring the background and skills in neuroscience, neuroimaging, and grant preparation needed to write a ROI proposal to adapt these cognitive tasks to a functional imaging setting to further elucidate the neural mechanisms of PD and DBS. -